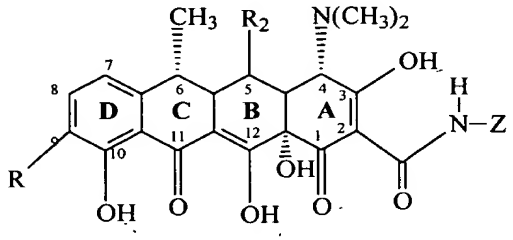
Claims

What is claimed is:

1. A 5,9-substituted tetracycline.

2. A compound of claim 1 of the following Formula I:



(I)

wherein R is alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl;

R^2 is alkanoyl; aroyl; alkaroyl; carbocyclic aryl, heteroaromatic, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl;

Z is hydrogen, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; aryalkyl, carbocyclic aryl, heteroalicyclic or heteroaromatic group; and pharmaceutically acceptable salts thereof.

3. A compound of claim 1 that is
5-propionate-9-t-butyl doxycycline;
9-chloro-t-butyl-5-propionate doxycycline;
9-t-butyl-6-alpha-deoxy-5-oxy-tetracycline;
9-t-butyl-5-oxytetracycline;
9-t-butyl-6-alpha-deoxy-5 -formyloxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5-acetoxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5-propionyloxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5 -phenylcarbonyloxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5 -benzylcarbonyloxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5 -dimethylaminocarbonyloxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5-cyclopentylcarbonyloxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5-cyclobutylcarbonyloxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5 -cyclohexylcarbonyloxy-tetracycline;
9-t-butyl-6-alpha-deoxy-5 -cycloheptylcarbonyloxy-tetracycline;
9-(chloro-t-butyl)-6-alpha-deoxy-5 -oxy-tetracycline;
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-oxy-tetracycline;
9-(amino)-t-butyl-6-alpha-deoxy-5-oxy-tetracycline;
9-[(piperidino)-t-butyl]-6-alpha-deoxy-5-oxy-tetracycline;
9-[(diethylamino)-t-butyl]-6-alpha-deoxy-5-oxy-tetracycline;
9-[(dipropylamino)-t-butyl]-6-alpha-deoxy-5-oxy-tetracycline;
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-formyloxy-tetracycline;
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5 -acetoxy-tetracycline;
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-propionylcarbonyloxy-tetracycline;
9-[(dimethylamIno)-t-butyl]-6-alpha-deoxy-5-phenylcarbonyloxy-tetracycline;
9-[(dimethylamino)-t-butyl] -6-alpha-deoxy-5-benzylcarbonyloxy-tetracycline;
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5 -dimethylaminocarbonyloxy-tetracycline;
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-cyclopentylcarbonyloxy-tetracycline;
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-cyclobutylcarbonyloxy-tetracycline;
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-cyclohexylcarbonyloxy-tetracycline; or
9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-cycloheptylcarbonyloxy-tetracycline; and pharmaceutically acceptable salts thereof.

4. The compound of claim 2 wherein R is alkyl having 1 to about 20 carbon atoms; alkenyl having 2 to about 20 carbon atoms; alkynyl having 2 to about 20 carbon atoms; alkoxy having 1 to about 20 carbon atoms; alkylthio having 1 to about 20 carbon atoms; alkylsulfinyl having from 1 to about 20 carbon atoms; alkylsulfonyl having from 1 to about 20 carbon atoms; alkylamino having from 1 to about 20 carbon atoms; or aryalkyl;

R^2 is alkyl having 1 to about 20 carbon atoms; alkenyl having 2 to about 20 carbon atoms; alkynyl 2 to about 20 carbon atoms; alkoxy 1 to about 20 carbon atoms; alkylthio having 1 to about 20 carbon atoms; alkylsulfinyl having from 1 to about 20 carbon atoms; alkylsulfonyl having from 1 to about 20 carbon atoms; alkylamino having from 1 to about 20 carbon atoms; or aryalkyl; alkanoyl from 1 to about 20 carbon atoms; aroyl; alkaroyl; carbocyclic aryl, heteroaromatic; and

Z is hydrogen, alkyl having 1 to about 20 carbon atoms; alkenyl having 2 to about 20 carbon atoms; alkynyl 2 to about 20 carbon atoms; alkoxy 1 to about 20 carbon atoms; alkylthio having 1 to about 20 carbon atoms; alkylsulfinyl having from 1 to about 20 carbon atoms; alkylsulfonyl having from 1 to about 20 carbon atoms; alkylamino having from 1 to about 20 carbon atoms; aryalkyl; carbocyclic aryl, or an heteroalicyclic group.

5. The compound of claim 2 wherein R is alkyl having 1 to about 12 carbon atoms; alkenyl having 2 to 12 about carbon atoms; alkynyl having 2 to 12 about carbon atoms; alkoxy having 1 to about 12 carbon atoms; alkylthio having 1 to about 12 carbon atoms; alkylsulfinyl having 1 to about 12 carbon atoms; alkylsulfonyl having 1 to about 12 carbon atoms; alkylamino having 1 to about 12 carbon atoms; or benzyl;

R^2 is alkyl having 1 to about 12 carbon atoms; alkenyl having 2 to 12 about carbon atoms; alkynyl having 2 to 12 about carbon atoms; alkoxy having 1 to about 12 carbon atoms; alkylthio having 1 to about 12 carbon atoms; alkylsulfinyl having 1 to about 12 carbon atoms; alkylsulfonyl having 1 to about 12 carbon atoms; alkylamino having 1 to about 12 carbon atoms; benzyl; aroyl; alkaroyl; carbocyclic aryl, heteroaromatic; and Z is hydrogen.

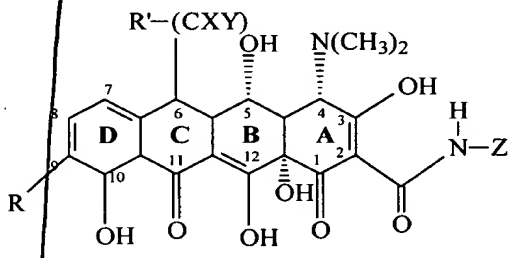
6. The compound of claim 2 wherein R and/or R^2 is selected from the group consisting of t-butyl; chloro-t-butyl; (dimethylamino)-t-butyl; propionate; piperidinoethyl; formyloxy; acetoxy; propionyloxy; phenylcarbonyloxy; benzylcarbonyloxy; piperidino; amino; diethylamino; dipropylamino;

acetylcarbonyloxy; propionylcarbonyloxy; phenylcarbonyloxy; benzylcarbonyloxy; dimethylaminocarbonyloxy; cyclopentylcarbonyloxy; cyclobutylcarbonyloxy; cyclohexylcarbonyloxy; cycloheptylcarbonyloxy; and Z is hydrogen.

7. The compound of claim 1, wherein said compound is selected from the group consisting of 5-propionate-9-t-butyl doxycycline; 9-t-butyl-6-deoxy-5-propionylcarbonyloxytetracycline, 9-t-butyl-6-deoxy-5-acetylcarbonyloxytetracycline, 9-t-butyl-6-deoxy-5-cyclobutylcarbonyloxytetracycline, and pharmaceutically acceptable salts thereof.

8. A 9,13-substituted tetracycline compound.

9. A compound of claim 8 that is of the following Formula II:



(II)

wherein R is alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl;

R^1 is hydrogen, hydroxy, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl;

X and Y are each independently hydrogen; halogen; hydroxyl; cyano, sulfhydryl; amino; alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl;

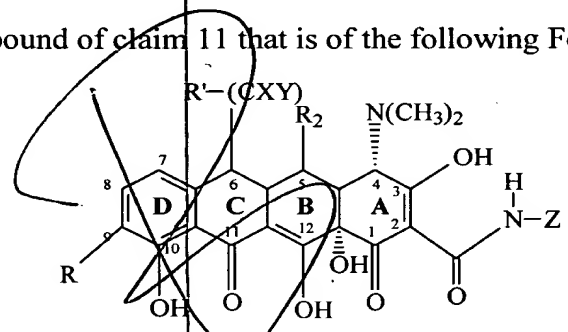
Z is hydrogen, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; aryalkyl, carbocyclic aryl, heteroalicyclic or heteroaromatic group; and pharmaceutically acceptable salts thereof.

10. A compound of claim 8 that is:
13-cyclopentylthio-9-t-butyl-5-oxy-tetracycline;
13-methylthio-9-t-butyl-5-oxy-tetracycline;
13-ethylthio-9-t-butyl-5-oxy-tetracycline;

13-propylthio-9-t-butyl-5-oxy-tetracycline;
13-isopropylthio-9-t-butyl-5-oxy-tetracycline;
13-butylthio-9-t-butyl-5-oxy-tetracycline;
13-isobutylthio-9-t-butyl-5-oxy-tetracycline;
13-pentylthio-9-t-butyl-5-oxy-tetracycline;
13-isopentylthio-9-t-butyl-5-oxy-tetracycline;
13-cyclobutylthio-9-t-butyl-5-oxy-tetracycline;
13-cyclopentylthio-9-t-butyl-5-oxy-tetracycline;
13-cyclohexylthio-9-t-butyl-5-oxy-tetracycline;
13-phenylthio-9-t-butyl-5-oxy-tetracycline;
13-(3,4-dichlorophenyl)thio-9-t-butyl-5-oxy-tetracycline;
13-benzylthio-9-t-butyl-5-oxy-tetracycline;
13-(4-chlorobenzyl)thio-9-t-butyl-5-oxy-tetracycline;
13-(3,4-dichlorobenzyl)thio-9-t-butyl-5-oxy-tetracycline;
13-(4-methoxybenzyl)thio-9-t-butyl-5-oxy-tetracycline;
13-(2,3-dihydroxypropyl)thio-9-t-butyl-5-oxy-tetracycline; and
5-propionate-13-cyclopentylthio-9-t-butyl oxytetracycline;
5-propionate-13-cyclopentylthio-9-piperidinoethyl oxytetracycline;
and pharmaceutically acceptable salts thereof.

11. A 5,9,13-substituted tetracycline.

12. A compound of claim 11 that is of the following Formula III:



(III)

wherein R is alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl;

R^2 is alkanoyl; aroyl; alkaroyl; carbocyclic aryl, heteroaromatic, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl such as benzyl;

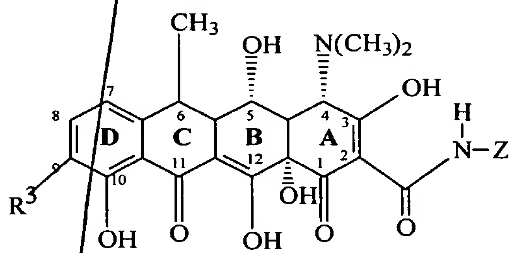
X and Y are each independently hydrogen; halogen; hydroxyl; cyano, sulfhydryl; amino; alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl;

Z is hydrogen, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; aryalkyl, carbocyclic aryl, heteroalicyclic or heteroaromatic group; and pharmaceutically acceptable salts thereof.

13. A compound of claim 11 that is:
13-cyclopentylthio-9-t-butyl-5-formyloxy-tetracycline;
13-methylthio-9-t-butyl-5-acetoxy-tetracycline;
13-ethylthio-9-t-butyl-5-propionylcarbonyloxy-tetracycline;
13-propylthio-9-t-butyl-5-butanylcarbonyloxy-tetracycline;
13-isopropylthio-9-t-butyl-5-cyclopentylcarbonyloxy-tetracycline;
13-butylthio-9-t-butyl-5-cyclohexylcarbonyloxy-tetracycline;
13-isobutylthio-9-t-butyl-5-cycloheptylcarbonyloxy-tetracycline;
13-pentylthio-9-t-butyl-5-formyloxy-tetracycline;
13-isopentylthio-9-t-butyl-5-acetoxy-tetracycline;
13-cyclobutylthio-9-t-butyl-5-propionylcarbonyloxy-tetracycline;
13-cyclopentylthio-9-t-butyl-5-cyclopentanylcarbonyloxy-tetracycline;
13-cyclohexylthio-9-t-butyl-5-cyclohexylcarbonyloxy-tetracycline;
13-phenylthio-9-t-butyl-5-phenylacetylcarbonyloxy-tetracycline;
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-formyloxy-tetracycline;
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-acetoxy-tetracycline;
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-propionylcarbonyloxy-tetracycline;
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-phenylcarbonyloxy-tetracycline;
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5 -benzylcarbonyloxy-tetracycline;
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-dimethylamino carbonyloxy-tetracycline;
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-cyclopentyl carbonyloxy-tetracycline;
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-cyclobutyl carbonyloxy-tetracycline;

13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-S-cyclohexyl carbonyloxy-tetracycline; or
13-cyclopentylthio-9-[(dimethylamino)-t-butyl]-6-alpha-deoxy-5-cycloheptyl carbonyloxy-tetracycline; and pharmaceutically acceptable salts thereof.

14. A compound of the following Formula IV:



(IV)

wherein R^3 is alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an aryalkyl;

Z is hydrogen, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; aryalkyl, carbocyclic aryl, heteroalicyclic or heteroaromatic group; and pharmaceutically acceptable salts thereof.

15. A compound of claim 14 which is
9-t-butyl tetracycline;
9-t-butyl anhydrotetracycline;
9-t-butyl minocycline; and pharmaceutically acceptable salts thereof.

16. The compound of claim 14 wherein R^3 is alkyl having 1 to about 20 carbon atoms; alkenyl having 2 to about 20 carbon atoms; alkynyl having 2 to about 20 carbon atoms; alkoxy having 1 to about 20 carbon atoms; alkylthio having 1 to about 20 carbon atoms; alkylsulfinyl having from 1 to about 20 carbon atoms; alkylsulfonyl having from 1 to about 20 carbon atoms; alkylamino having from 1 to about 20 carbon atoms; or aryalkyl; and

Z is hydrogen, alkyl having 1 to about 20 carbon atoms; alkenyl having 2 to about 20 carbon atoms; alkynyl 2 to about 20 carbon atoms; alkoxy 1 to about 20 carbon atoms; alkylthio having 1 to about 20 carbon atoms; alkylsulfinyl having from 1 to about 20 carbon atoms; alkylsulfonyl having from 1 to about 20 carbon atoms; alkylamino having from 1 to about 20 carbon atoms; aryalkyl; carbocyclic aryl, or an heteroalicyclic group.

17. The compound of claim 14 wherein R^3 is alkyl having 1 to about 12 carbon atoms; alkenyl having 2 to 12 about carbon atoms; alkynyl having 2 to 12 about carbon atoms; alkoxy having 1 to about 12 carbon atoms; alkylthio having 1 to about 12 carbon atoms; alkylsulfinyl having 1 to about 12 carbon atoms; alkylsulfonyl having 1 to about 12 carbon atoms; alkylamino having 1 to about 12 carbon atoms; or benzyl; and Z is hydrogen.

18. The compound of claim 14 wherein R^3 is selected from the group consisting of t-butyl; chloro-t-butyl; (dimethylamino)-t-butyl; methylcyclohexyl; methylcyclobutyl; methylpentyl; bromomethylpentyl; nitromethylpentyl; and acetoxymethylpentyl.

19. The compound of claim 14, wherein said compound is selected from the group consisting of 9-t-butyl-6-deoxy-5-hydroxytetracycline, 9-[1'-(1'-methyl)cyclohexyl]-6-deoxy-5-hydroxytetracycline, 9-[1'-(1'-methyl)cyclopentyl]-6-deoxy-5-hydroxytetracycline, 9-[1'-(1'-methyl)cyclobutyl]-6-deoxy-5-hydroxytetracycline, 9-[2'-(2'-methyl)pentyl]-6-deoxy-5-hydroxytetracycline, 9-[4'-(1'-bromo-4'-methyl)pentyl]-6-deoxy-5-hydroxytetracycline, 9-[4'-(1'-dimethylamino-4'-methyl)pentyl]-6-deoxy-5-hydroxytetracycline, 9-[4'-(1'-pyrrolidinyl-4'-methyl)pentyl]-6-deoxy-5-hydroxytetracycline, 9-[4'-(1'-cyano -4'-methyl)pentyl]-6-deoxy-5-hydroxytetracycline, 9-[4'-(1'-nitro -4'-methyl)pentyl]-6-deoxy-5-hydroxytetracycline, 9-[4'-(1'-acetoxy -4'-methyl)pentyl]-6-deoxy-5-hydroxytetracycline); 9-t-butyl tetracycline; 9-t-butyl anhydrotetracycline; 9-t-butyl minocycline; and pharmaceutically acceptable salts thereof.

20. A method for treating against a targeted microogranism comprising administering to the microorganism a compound of any one of claims 1 through 19.

21. A method for treating against bacteria comprising administering to the bacteria a compound of any one of claims 1 through 19.

22. A method for treating a mammal suffering from or susceptible to a microorganism infection or disease associated therewith comprising administering to the mammal a compound of any one of claims 1 through 19.

23. A method for treating a mammal suffering from or susceptible to bacteria infection comprising administering to the mammal a compound of any one of claims 1 through 19.

24. The method of claim 22 or 23 wherein the mammal is a human.

25. The method of any one of claims 20-22 wherein the microorgansim or bacteria is tetracycline sensitive.

26. The method of any one of claims 20-22 wherein the microorgansim or bacteria is tetracycline resistant.

27. The method of any one of claims 20-26 wherein the bacteria is *E. coli., S. aureus* or *E. faecalis.*

28. A method for converting tetracycline resistant bacteria into tetracycline resistant bacteria, comprising

a) contacting the resistant bacteria with a predetermined quantity of a compound of any one of claims 1 through 11, and

b) concomitantly administering to the bacteria a predetermined quantity of a tetracycline-type compound that is different than the compound of step a).

29. A pharmaceutical composition of any one of claims 1 through 19.